Has the model figured in this paper any value either to confirm or to disprove the linear hypothesis? It does not, like the models of chromosomes 1 and 3, show the genes in a curved band lying in one plane. But it does show them lying roughly in a linear chain winding cork-screw fashion through the model. If all wires over 40 inches long were cut, the system would straighten out so as to approach a linear arrangement. I conclude that the model supports the linear hypothesis, if it be supposed that the longer distances have been shortened by double crossing-over, and that map distances in such cases should exceed observed cross-over percentages.

[1] These PROCEEDINGS, **5,** 25, 32, and 500.

[2] *Carnegie Inst. Washington, Publ.* **237,** 1916.

[3] *Genetics,* **3,** 1918 (107–134).

[4] Bridges, C. B., and Morgan, T. H., "The Second Chromosome Group of Mutant Characters," *Carnegie Inst. Washington, Publ.* **278,** 1919 (123–304).

[5] Gowen, J. W., "A Biometrical Study of crossing Over." *Genetics,* **4**; May, 1919 (205–250).

[6] These PROCEEDINGS, **5,** May, 1919.

[7] Haldane, J. B. S., *Genetics,* **8,** Sept., 1919 (306).

THE DEVELOPMENT OF CONNECTIVE TISSUE IN THE AMPHIBIAN EMBRYO

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The researches[1] in which the author has been engaged for several years have shown, in brief, that the structure of the plasma clot of frog's blood is of such a nature that when influenced by the proper mechanical factors, e.g., tension or pressure, its structure will be radically changed. In cases of this kind a fusion and consolidation of the minute elements of the clot will take place and, as a result, long fibers will be formed which unite in wavy bundles, anastomose with other bundles and ramify in various directions throughout the clot, thus resulting in the formation of a material which, at least in its morphology, is like certain types of connective tissue. In wounds in frog's skin, the experiments showed that a fibrous tissue formed from a plasma clot functioned, at least temporarily, as a normal connective tissue and there was no evidence to show that it would ever be replaced.

The above results led naturally to the question as to whether a similar process normally takes place in the histogenesis of connective tissue in amphibian embryos. The results obtained from these investigations are as follows:

1. The primitive forerunner of connective tissue in frog embryos is an amorphous, gelatinous material which, because of the fact that it stains

very lightly in the early stages by any of the numerous methods tried, is difficult to detect. This ground substance can be demonstrated around the notochord soon after it is formed and shortly before the embryo has reached the tail bud stage. A little later this material, which is to form a part at least of the connective tissues, surrounds the medullary cord and a layer of it, following the body wall, extends ventrally on either side and in time completely encircles the body cavity. The formation of this matrix around the notochord occurs before there is any syncytium of the mesenchyme cells in this region. In fact, at this stage, the cells here present have not yet assumed the shape of typical mesenchyme cells which later appear. It is evident, therefore, that this primitive ground substance of connective tissue has arisen as an intercellular secretion of the embryonic cells[2] and not by a syncytial fusion of cytoplasm.

2. The ground substance having been formed, cells begin to move into it and wander through it. These are spherical at first but, as they move through the ground substance, they soon change into various shapes, becoming stellate, spindle-shaped, etc. The study of the sections shows that, in general, individual cells do not separate from the cell masses and move out into the various cavities and open spaces of the embryo until after the formation of the secreted ground substance which is the forerunner of the connective tissues. The present work, therefore, adds additional evidence in support of the conclusions which Harrison[3] and others have reached with regard to the stereotropism of cells in tissue cultures. Cells, whether in tissue cultures or in the developing embryo, have need of a supporting framework of some kind in order for migration from the main masses to take place.

3. The connective tissue fibers begin to arise in the ground substance soon after it has formed. In some cases, they form in the ground substance in regions which are free from cells so that it is very clear that they have not arisen by any intracellular action. Instances can be noted in which it appears that the fibers are formed by a gradual transformation of the ground substance, first, into a delicate net-like structure and then into the long fibers which are typical of connective tissue. In its morphological features, at least, this process gives evidence of being identical with the one previously observed in the transformation of the plasma clot.

4. In other regions of the ground substance into which the cells have wandered, the formation of the fibers can also be shown to be due to changes in the ground substance and not to a sloughing off of the cell protoplasm. A differential stain, such as Mallory's connective tissue stain, shows very clearly the limits of the cell cytoplasm and the beginning of the ground substance. In many cases the paths of the cells can be traced through the ground substance and the possibility arises that, in their movements through the ground substance, they may give off secretions which play a part in the final chemical constitution of the fibers.

However, the fact that the fibers can form in a cell-free ground substance shows that no part of the cell cytoplasm is necessary for their differentiation from the ground substance.

5. Any satisfactory theory of connective tissue formation must take into account the well-established fact that the great mass of the connective tissues, both ground substance and fibers, is formed when not in contact with cells. The adherents of the intracellular theory of connective tissue formation, holding that both ground substance and fibers are living material, although of a different grade from that in cells, maintain that the embryonic connective tissue after it has been formed by an intracellular action has the power to grow through the assimilation of food material, and the ability to differentiate new fibers.[4]

6. The results of the present researches may be summarized as follows:

(*a*) The origin of connective tissue lies in an intercellular secretion of the embryonic cells. This secretion constitutes the ground substance of the connective tissues and it increases in amount during development not by an assimilation of food materials and consequent growth but by the continued and additional secretions given off by the embryonic cells.

(*b*) This ground substance secreted by the cells is of such a nature that, under the influence of various chemical and mechanical factors, it forms the connective tissue fibers by means of a consolidation of the minute elements of which it is composed in apparently the same way that a transformation of the plasma clot occurs.

[1] Baitsell, G. A., (*a*) *J. Exper. Med.*, **21**, 1915 (455); (*b*) *Ibid.*, **23**, 1916 (739); (*c*) *Amer. J. Physiol.*, **44**, 1917 (109).

[2] The presence of a primitive ground substance has been demonstrated by various investigators. E.g., see Merkel, F., *Anat. Hefte*, **38**, 1908 (321); and Szily, A., *Ibid.*, **37**, 1907 (649). Both of these articles contain a full review of the literature.

[3] Harrison, R. G., *J. Exper. Zoöl.*, **17**, 1914 (521).

[4] E.g., see Heidenhain, M., *Plasma und Zelle*, pp. 33, 38, etc.

CALCIUM AND MAGNESIUM METABOLISM IN CERTAIN DISEASES

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We wish to present some observations upon calcium and magnesium metabolism in leprosy and in multiple exostosis.

Clinically, leprosy is characterized by a *loss* from the body of bone salts; in multiple exostosis bone salts are *added* to the organism for the calcification of the new growths. It is thus apparent that in these two abnormal conditions the processes involved in calcium and magnesium